A Review of Mortality in Tumorigenicity Studies, Completed over the Period 1987 to 2000, using the Charles River Original or International Genetic Standard Sprague-Dawley Rat.

W N Hooks and R J Harling.

Huntingdon Life Sciences Ltd.,
Huntingdon, Cambridgeshire, UK.

Huntingdon
Life Sciences
Working for a better future

A Review of Mortality in Tum using the Charles River Orig

W N Hooks and R J Harling.

ABSTRACT

At Huntingdon Life Sciences, the mortality data have been analysed from the control groups of 83 tumorigenicity studies using the original or International Genetic Standard (IGS) strain designations of Sprague-Dawley rat, Crl:CD® BR (VAF). The data obtained from the IGS rat have been closely monitored since the introduction of this new strain designation in 1996 and 13 studies completed over 1998 to 2000 have been compared against up to 70 studies using the original strain designation (completed over 1987 to 1997). Low protein maintenance diet was used in these dietary and oral gavage studies.

The analyses have indicated that the IGS rat is showing a similarly high mortality pattern to that seen in the original strain studies completed over the period 1996-97, but an increased pattern when compared with studies completed 1993-95. In the original rat studies, review of the terminal mortality against time has demonstrated an increasing trend towards higher values over the period of 1987 to 1997, particularly in females. The 13 completed IGS rat studies show a similar trend to the original rat studies.

From the results currently available, it can be concluded that the IGS rat is not remarkably different from the original strain of rat, showing the same high mortality pattern, particularly in female rats.

INTRODUCTION

The Charles River International Genetic Standard (IGS) strain designation of Sprague-Dawley rat Crl:CD® BR (VAF) superseded the original strain designation of rat from 1996. At these laboratories, the data obtained from tumorigenicity studies using the IGS rat have been closely monitored and compared with data obtained from the original strain designation of Sprague-Dawley rat [1, 2, 3]. This review was conducted to compare the mortality pattern of the increasing number of IGS rat tumorigenicity studies (completed in 1998 to 2000) against up to 70 studies (completed 1987 to 1997) using the original strain designation of Sprague-Dawley rat. Low protein maintenance diet was used in these dietary or oral gavage studies.

References:

1. Hooks, W.N. and Saunders, M.D. Toxicology Letters 1/85 (1998).
2. Hooks, W.N. Biological Reference Data on CD (SD) IGS Rats 1998, edited by Dr T Matsuzawa, Yamanouchi Pharmaceutical Co. Ltd., Japan.
3. Hooks, W.N. Biological Reference Data on CD (SD) IGS Rats 1999, edited by Dr T Matsuzawa, Yamanouchi Pharmaceutical Co. Ltd., Japan.

PROCEDURAL DETAILS

Animals

- Sprague-Dawley Crl:CD® BR (VAF) rats obtained from Charles River breeding laboratories in the UK or USA and maintained as control rats for tumorigenicity studies.
- Approximately 6 weeks of age at start of study, mainly housed 5 rats/cage (singly housed studies are indicated, where appropriate).
- Maintained under standard laboratory conditions, with target ranges of 19-23°C for temperature and 40-70% for relative humidity. A 12 hour light and 12 hour dark cycle was maintained.

Study Design

- **Studies reviewed:**

  Tumorigenicity studies terminating between 1987 and 2000.

- **Number of control groups reviewed:**

  Original strain 70;
  IGS strain 13.
  At least 50 males and 50 females in each control group.

- **Route of administration:**

  Dietary and oral gavage.

- **Diet (fed *ad libitum*):**

  Ground rodent maintenance diet
  (Special Diets Services Rat and Mouse No. 1:
  typically 14.5% protein, 3% fat, 4% fibre).

Data presentation and analysis:

- Mean terminal (Week 104) percentage mortality values are presented over selected time periods, both graphically (Figure 1, all studies) and in Table 1 (detailing the route of administration and housing conditions).
- The percentage mortality for each control group at study Week 104 is presented chronologically between 1987 and 2000. A regression analysis of mortality against time was performed on the data followed by a two-tailed t-test of the slope; P-values and the direction of slope are presented.
- The mortality pattern is presented over the period of Weeks 52 to 104 only, as mortality in the first year is low. Studies terminated from 1993 to 2000 are compared. Data from ongoing IGS rat studies are also included in the assessment.

norigenicity Studies, Completed over the Period 1987 to 2000, iginal or International Genetic Standard Sprague-Dawley Rat.

Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, UK.

RESULTS

Figure 1: Mortality at Week 104

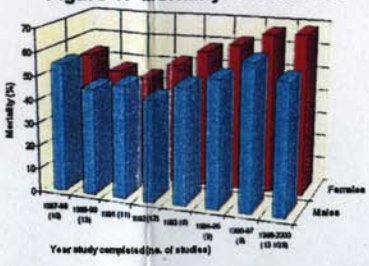


Figure 1: In order to place the Sprague-Dawley rat mortality values in historical perspective, the terminal mortality values are presented over selected time periods from 1987. The trend towards increasing mortality is apparent, particularly from 1993 in female rats. The IGS rat studies (completed 1998-2000) show a similar trend, particularly in females.

Figures 2 & 3: In order to test the apparent trend statistically, the individual terminal mortality values were plotted against time and a regression analysis performed. The statistical analysis of the trend line for all studies completed over the period of 1987 to 1997 has shown a positive trend in both male and female rats (linear regression line presented, P=0.0520 for males and P=0.0001 for females). Similar findings were apparent when gang housed dietary studies only were compared over this period (P=0.0433 for males and P=0.0008 for females) and when all studies were compared over 1993-97 (P=0.0274 for males and P=0.0391 for females). The 13 IGS rat studies completed 1998-2000 were not included in the statistical analysis, but the trend towards higher terminal mortality in these studies is similar to that of the original strain designation of rat, particularly in females.

Figure 2: Mortality distribution at Week 104 - males

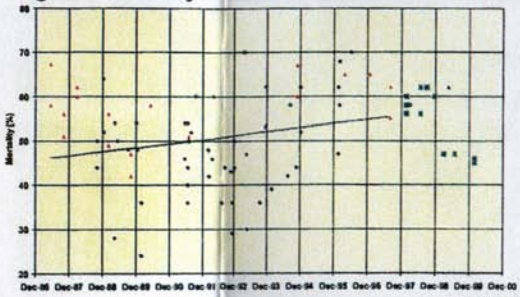
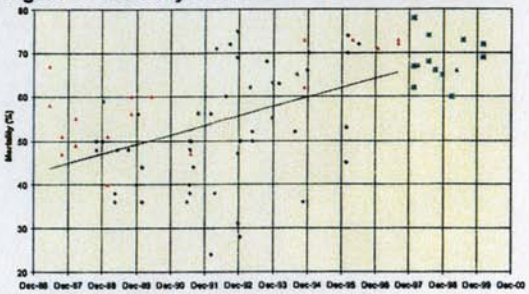


Figure 3: Mortality distribution at Week 104 - females



Time (date studies completed, 1987 - 2000)

Dietary/gang housed; Dietary/gang housed (IGS); Dietary/singly housed; Oral gavage/gang housed (IGS); Oral gavage/gang housed; Oral gavage/singly housed (IGS); Oral gavage/singly housed; Linear regression line

Figures 4 & 5: In the original strain designation of rat, studies completed 1996-97 have shown a higher mortality pattern over the Weeks 52 to 104, particularly in female rats, when compared with studies completed over 1993-95. The mortality pattern of the IGS rat studies (including ongoing studies) is similar to that of studies completed over 1996-97, but higher than studies completed over 1993-95.

Figure 4: Mortality over Weeks 52 to 104 - males

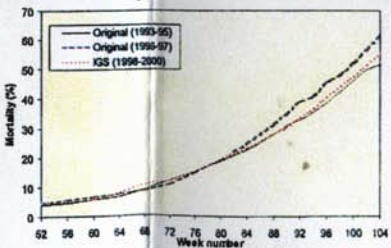
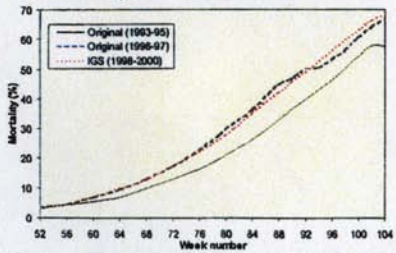


Figure 5: Mortality over Weeks 52 to 104 - females



DISCUSSION

The analyses performed in this review have indicated that the IGS rat is showing a similarly high mortality pattern to that seen in the original strain studies completed over the period 1996-97, but an increased pattern when compared with studies completed 1993-95. Review of the terminal mortality against time, for studies using the original strain of rat, has demonstrated an increasing trend towards higher values over the period of 1987 to 1997, particularly in females. In the 13 completed IGS rat studies, the females are showing a similar trend to the original rat studies. However, in the males, there is an indication of improvement with the four most recently completed dietary studies showing mortality values of less than 50%.

From the results currently available, it can be concluded that the IGS rat is not remarkably different from the original strain of rat, showing the same high mortality pattern, particularly in female rats.

Table 1 - Mortality (%) at Week 104 for dietary and oral gavage studies

Studies completed/ Strain designation		Dietary/ gang housed		Dietary/ singly housed		Oral gavage/ gang housed		Oral gavage/ singly housed		All Studies	
		M	F	M	F	M	F	M	F	M	F
1987-92/ Original	Mean	45	46	56	58	54	53	60	71	48	49
	SD	8.6	11.9	5.7	2.1	5.8	7.4	-	-	9.0	11.5
	n	31	31	2	2	12	12	1	1	46	46
1993-95/ Original	Mean	46	59	61	61	64	68			52	60
	SD	11.0	11.7	7.2	4.3	4.9	7.8			12.1	9.8
	n	9	9	4	4	2	2	0	0	15	15
1996-97/ Original	Mean	61	63			62	72			61	67
	SD	9.2	13.0			4.7	1.0			7.1	10.5
	n	5	5	0	0	4	4	0	0	9	9
1998-2000/ IGS	Mean	54	69			62	66	58	67	55	69
	SD	6.8	5.4			-	-	-	-	6.6	5.4
	n	11	11	0	0	1	1	1	1	13	13

M Male rats, F Female rats,
SD Standard deviation, n Number of studies

Table 1: For comparative purposes, the mean mortality, together with the Standard deviation and number, are detailed for the different study types over selected time periods.